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PART III

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

ANIMAL FEEDS CONTAINING PENICILLIN AND TETRACYCLINE

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 558]

[Docket No. 77N-0318]

NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

Animal Feeds Containing Penicillin and Tetracycline

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Commissioner of Food and Drugs, based on the recommendations of the National Advisory Food and Drug Committee concerning evidence of the development and transfer of antibiotic resistance, is proposing to limit the distribution of animal feed premixes containing penicillin and tetracycline (chlortetracycline and oxytetracycline) to feed mills that hold approved medicated feed applications which permit the mills to manufacture such medicated feeds. He is also proposing to restrict further the distribution of such feeds to the order of a licensed veterinarian as part of the record maintenance requirements of the Federal Food, Drug, and Cosmetic Act.

DATES: Written comments by April 20, 1978. The Commissioner will also hold two informal public hearings in accord with the provisions of 21 CFR Part 15, to provide the opportunity for oral comments on the proposal by interested persons. The hearings will be held in agricultural areas, and the time and place of those meetings will be announced in future FEDERAL REGISTER notices.

ADDRESS: Comments to the hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Gerald B. Guest, Bureau of Veterinary Medicine (HFV-130), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-4313).

SUPPLEMENTARY INFORMATION:

I. INTRODUCTION

A. REGULATORY BACKGROUND

Antibacterial drugs have been used at subtherapeutic levels (lower levels than those necessary to cure disease) in animal feed for over 25 years for growth promotion, improved feed efficiency, and disease prevention. Growth promotant benefits from this use were first observed when animals were fed the discard products from the fermentation process that was originally used in the manufacture of chlortetracycline; however, the precise mechanism of that action remains unclear.

Initially, antibiotics for use in animal feed were regulated under the provisions of section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357). Unlike the basic private licensing system applicable to new drugs, the provisions of section 507 created a public regulation or monograph system for regulating these products, in part because of the complexities in manufacturing the products and the lack of knowledge of their chemical structures. Antibiotic residues in food from food-producing animals were then regulated under the provisions of the act dealing with adulteration and misbranding. After enactment of the Food Additives Amendment of 1958 (Pub. L. 85-929), the residues were principally regulated by section 409 of the act (21 U.S.C. 348) which also establishes a public monograph system of premarket approval.

Under the antibiotic monograph procedure, the pioneer manufacturer generates and submits the basic safety and effectiveness data in a form FD-1675 (formerly FD Form 5). A regulation is subsequently published setting forth the standards of identity, strength, quality, and purity and the requirements for packaging and labeling which the product must meet. The Commissioner of Food and Drugs' approval of the same product made by another manufacturer is then conditioned solely upon a demonstration that it meets the requirements of the regulation, and this is normally accomplished by batch certification. Section 507(c) of the act, however, permits the Commissioner to exempt by regulation any drug or class of drugs from the certification requirement when he concludes that certification is unnecessary for the manufacture of the drugs. Antibiotics for use in animal feeds as feed ingredients were exempted from the certification requirement in 1951 by publication in the FEDERAL REGISTER of April 28, 1951 (16 FR 3647), and those for use as drugs were exempted in 1953 by publication in the FEDERAL REGISTER of April 22, 1953 (18 FR 2335). These are now set out in §§ 510.510 and 510.515 (21 CFR 510.510 and 510.515).

The Animal Drug Amendments (Pub. L. 90-399) consolidated the provisions of the act then dealing with the premarket approval of drugs intended for use in animals (sections 409, 505, and 507) into new section 512 (21 U.S.C. 360b), to more efficiently and effectively regulate these articles (Senate Committee on Labor and Public Welfare, Animal Drug Amendments of 1968, S. Rep. No. 1308, 90th Cong., 2d Sess. (1968)). One side effect of this legislation brought the manufacture of antibiotics under the same private licensing system applicable to new drugs (id; Hearing on S. 1600 and H.R. 3639 Before the Subcommittee on Health of the Senate Committee on Labor and Public welfare, 90th Cong., 2d Sess. (1968)). To efficiently accomplish this change, Pub. L. 90-399 contained a transition clause (section 108(b)) which provided that all prior approvals for the use of drugs in animals and animal feeds would continue in effect and be subject to change in accordance with the provisions of the basic act as amended. In summary, all persons legally marketing antibiotics under the provisions of sections 409, 505, and 507 of the act on August 1, 1969, the effective date of the Animal Drug Amendments of 1968, were awarded the equivalent of an approved new animal drug application (NADA); but all holders of such approvals were also subjected to all the requirements imposed by the act and regulations on such persons.

B. SAFETY CONCERNS

The Food and Drug Administration (FDA) first became concerned about the potential for harm to man and animals associated with subtherapeutic antibiotic use in animal feed in the mid-1960's, and it began to study the effects of low-level subtherapeutic feeding of antibiotics extensively. The agency supported research, held symposia, and consulted with outside experts to review these nonmedical uses of antibiotics in animal feeds. Following a report issued by the British Government Joint Committee (the Swann Committee), "On the Use of Antibiotics in Animal Husbandry and Veterinary Medicine," the Commissioner established a Task Force of scientists, with consultants from government, universities, and industry, to review comprehensively the use of antibiotic drugs in animal feeds in April 1970.

The Task Force's conclusions were published in a February 1, 1972 (37 FR 2444) notice of proposed rulemaking which initiated the mandatory testing procedure outlined in § 558.15 (21 CFR 558.15) to resolve conclusively the issues of safety surrounding the subtherapeutic use of antibiotics in animal feeds. The Task Force's principal conclusions were the following:

(1) The use of antibiotics and sulfonamide drugs, especially in growth promotant and subtherapeutic amounts, favors the selection and development of single and multiple antibiotic resistant and R-plasmid-bearing bacteria.

(2) Animals which have received either subtherapeutic and/or therapeutic amounts of antibiotic and sulfonamide drugs in feeds may serve as a

reservoir of antibiotic resistant pathogens and nonpathogens. These reservoirs of pathogens can produce human infections.

(3) The prevalance of multiresistant R-plasmid-bearing pathogenic and nonpathogenic bacteria in animals has increased and has been related to the use of antibiotics and sulfonamide drugs.

(4) Organisms resistant to antibacterial agents have been found on meat and meat products.

(5) There has been an increase in the prevalence of antibiotic and sulfonamide resistant bacteria in man.

(6) The Task Force also identified three areas of primary concern: human health hazards, animal health hazards, and antibiotic effectiveness; and it established guidelines to measure whether use of any antibiotic or antibacterial agent in animal feed presents a hazard to human and animal health.

Principally, the February 1972 proposal announced that all currently approved subtherapeutic uses of antibiotics, nitrofurans, and sulfonamides in animal feeds would be revoked unless data were submitted to resolve conclusively the issues concerning safety to man and animals in accordance with the Task Force guidelines. The notice also proposed to establish a time table for filing commitments, conducting studies, and submitting relevant data and information. Briefly, the guidelines may be summarized as follows:

HUMAN AND ANIMAL HEALTH SAFETY CRITERIA

1. Transfer of drug resistance: (a) An antibacterial drug fed at subtherapeutic levels to animals must be shown not to promote increased resistance to antibacterials used in human medicine. Specifically, increased multiple resistance capable of being transferred to other bacteria in animals or man should not occur. (b) If increased transferable multiple resistance is found in coliforms, studies may be done to show whether this resistance is transferable to man.

2. The *Salmonella* reservoir: The use of an antibacterial drug at subtherapeutic levels in animal feed must be shown not to result in (a) an increase in quantity, prevalence or duration of shedding of *Salmonella* in medicated animals as compared to nonmedicated controls; (b) an increase in the number of antibiotic resistant *Salmonella* or in the spectrum of antibiotic resistance; (c) disease (caused by *Salmonella* or other organisms) that is more difficult to treat with either the same medication or other drugs.

3. The use of subtherapeutic levels of an antibacterial drug should not enhance the pathogenicity of bacteria, e.g., by increasing enterotoxin production. The association of toxin-produced characteristics with transfer factors must be investigated in well-designed studies. (Final resolution of this question was not expected within the 2-year period. Drug sponsors were expected to show evidence of work underway which would lead toward answers to this question.)

4. An antibacterial drug used at subtherapeutic levels in the feed of animals shall not result in residues in food ingested by man which may cause either increased numbers of pathogenic bacteria or an increase in the resistance of pathogens to antibacterial agents used in human medicine. Hypersensitivity to residues was to be addressed by a literature survey.

The February 1972 proposal further addressed the issue of future antibiotic use in animal feed if the Commissioner were utlimately to conclude, after evaluating the data to be submitted, that the subtherapeutic use of antibiotics in animal feeds should be curtailed. The Commissioner proposed to restrict any remaining uses of antibiotics in animal feeds to short-term therapeutic use on the order of a licensed veterinarian.

Some 380 responses were received on the proposal, and the Commissioner promulgated the final order on April 20, 1973 (38 FR 9811.) One issue specifically discussed in the preamble to the final regulations was the practicality of the veterinarian's order option. The agency's Task Force on the Use of Antibiotics in Animal Feeds initially suggested this restriction, and the Commissioner agreed with it. He concluded that adopting this restriction would insure the continued availability of useful products while at the same time limiting the improper use of products that have exhibited a safety hazard.

With the promulgation of the final order, the requirements imposed became legally binding on all firms marketing antibacterial drugs for subtherapeutic use in feed. Therefore, in the FEDERAL REGISTER of August 6, 1974 (39 FR 28393), the Commissioner proposed to withdraw all approvals held by persons who had not complied with the initial requirement of filing commitments to conduct the necessary studies, and all such approvals were withdrawn by his order issued on February 25, 1976 (41 FR 8282). Thus, only those products now listed in Part 558 (21 CFR Part 558) can be legally marketed at this time.

By April 20, 1974, the date established for the first submissions of data under § 558.15, the Bureau of Veterinary Medicine had begun a review of the data submitted for penicillin and tetracycline (chlortetracyline and oxytetracycline), which are the most significant antibiotics used both subtherapeutically in animal feeds and in human medicine, and by April 20, 1975, data concerning the safety and efficacy criteria for all antibiotic and sulfonamide drugs had been received. At the Bureau's request, the Commissioner asked FDA's National Advisory Food and Drug Committee (NAFDC) to review the data and the issues involved and to make reommendations on the future uses of subtherapeutic antibiotics in animal feeds.

The NAFDC appointed a subcommittee of three members, the Antibiotics in Animal Feeds Subcommittee (AAFS), to work in conjunction with four expert consultants from disciplines related to the issue. The Bureau of Veterinary Medicine prepared detailed analyses of the evidence concerning penicillin and the tetracyclines which were presented to the AAFS during 5 days of open meetings. Comments were also heard at these meetings from the drug industry, animal scientists, and other interested parties. The Bureau prepared a comprehensive summary report for the subcommittee with tentative recommendations. Two additional meetings were held during which the subcommittee deliberated and proponents and opponents of subtherapeutic antibiotic use gave statements. In September 1976, the AAFS presented its preliminary report ot the parent committee (Ref. 1). The subcommittee made general recommendations on the future uses of antibiotics in animal feed and specific recommendations on the future use of penicillin and the tetracyclines.

For penicillin, the subcommittee recommended that FDA discontinue its use in all species for growth promotion and feed efficiency. It further recommended that use of penicillin be discontinued in all species for disease prevention where effective substitutes are available.

The recomendations of the AAFS concerning continued tetracycline use were less stringent. It recommended that FDA discontinue tetracycline use for growth promotion, feed efficiency, and disease prevention in all species where effective substitutes are available. The subcommitee also recommended that the remaining subtherapeutic tetracycline uses be limited to those periods of time when a particular animal species is threatened with a specific animal disease.

The subcommitee's general recommendations were far ranging. Recognizing that a potential for harm is inherent in widespread use of antibiotics in animal feeds, it recommended that FDA establish regulatory measures to assure that antibacterial drugs are used judiciously in animal feeds by limiting sale of tetracycline- and penicillin-containing products to feed mills and producers who hold an approved medicated feed application. The subcommitee recognized that this action would remove these products from direct dispensing by veterinarians who do not own registered feed mills, and accordingly the subcommitee suggested that the order of a licensed veterinarian be incorporated into the distribution system. It further recommended careful monitoring procedures to assure compliance with the proposed use restrictions. The remaining recommendations concerned future monitoring, research, and goals.

At its January 24, 1977 meeting, the NAFDC agreed that a potential for harm exists with subtherapeutic antibiotic use in animal feed and accepted both the subcommittee's recommendation on penicillin use and the basic context of the general recommendations. But, for tetracyclines, the committee concluded that only distribution be restricted in conjunction with the conditions imposed by the general recommendations (Ref. *2*). The Commissioner agreed with the NAFDC's recommendations on penicillin. However, he concluded that more stringent action against the use of tetracycline was necessary, and at the April 15, 1977 NAFDC meeting he announced that FDA would propose to discontinue all nonessential tetracycline uses in animal feed.

The Commissioner also recognized the importance of the NAFDC's general recommendations to restrict the distribution and unsupervised use of these antibiotics in animal feeds. For this reason, he announced that FDA would propose to add the requirements for an approved medicated feed application (Form FD-1800) and the veterinarian's order (1) to insure, to the extent possible, that the drugs will be placed in the hands of individuals with training and background who are qualified to administer the drug products, (2) to assist the use of the most effective level of antibiotic for the shortest time necessary to achieve the desired results, and (3) to insure that a valuable management tool, i.e., the tetracyclines, continues to be available when necessary (Ref. *3*).

Since that time, FDA has initiated a series of administrative actions that ultimately propose to eliminate all uses of penicillin- and tetracycline-containing medicated animal feeds that have not been shown to be safe and effective, or for which there are safe and effective alternatives. This will assure that any potential for harm associated with the use of these products will be minimized if not eliminated.

In the FEDERAL REGISTER of May 27, 1977 (42 FR 27264), the Commissioner issued a call for data on the potential environmental impact of FDA's proposed actions. He further announced that the Bureau of Veterinary Medicine would propose (1) to terminate all subtherapeutic uses of penicillin in animal feed, (2) to restrict the use of tetracyclines to situations where there are no viable alternatives, (3) to impose restrictions on the distribution and the uses of penicillin and tetracycline in animal feed, and (4) to expedite the drug efficacy study implementation notices proposing to withdraw approval of all penicillin and tetracycline combination products that lack substantial evidence of effectiveness.

The Director of the Bureau of Veterinary Medicine, in the FEDERAL REGISTER of June 10, 1977 (42 FR 2999), then issued a notice of opportunity for hearing proposing to withdraw approval of the NADA's for all penicillin-streptomycin premixes intended for use in animal feed on the ground that new information now before him indicates that they lack substantial evidence of the effectiveness that is required for their indications for use.

Next, in the FEDERAL REGISTER of August 30, 1977 (42 FR 43772), the Director issued a notice of opportunity for hearing proposing to withdraw approval of all NADA's for penicillin-containing new animal drugs intended for use in animal feed principally because the evidence surrounding this use demonstrates that they have not been shown to be safe. He issued a similar notice of opportunity for hearing concerning certain subtherapeutic uses of tetracycline in animal feed on October 21, 1977 (42 FR 56264).

II. FUNCTION OF THIS NOTICE

The function of this notice is to provide a forum for public debate on the need to revise FDA's prior policy on the control and distribution of penicillin and tetracycline in animal feed. These products are now available without the need for a veterinarian's order, and no approved application is required to manufacture a medicated feed containing them. The Commissioner is proposing to impose regulatory procedures that will eliminate the routine and unnecessary use of antibiotics in animal feeds. The FDA Task Force on the Use of Antibiotics in Animal Feeds, the AAFS, and the NAFDC have all recommended this course of action independently from recommendations about the safety of these drugs, and the Commissioner agrees that dealing with the distribution and control issue separately is the appropriate way to proceed. As the discussion in Part III of this preamble outlines, the evidence before FDA demonstrates that a potential for harm to animals and man exists from the development of R-plasmid-mediated resistance to antibacterial agents which may be aggravated by uncontrolled subtherapeutic use of these antibiotics in animal feed. An effort must be made to assure the future utility of these life-saving products because use of the antibiotics is extensive for both humans and animals.

In 1960, the annual production of antibiotics in the United States was 4.16 million pounds, of which 2.95 million pounds were used for therapeutic purposes in human and veterinary medicine and 1.20 million pounds were added to animal feed. By 1970, 9.6 million pounds were used in human and veterinary medical pharmaceuticals, and the animal feed additive use was 7.3 million pounds. Moreover, according to "Synthetic Organic Chemicals, United States Production and Sales (1971-1975)," U.S. International Trade Commission Publication 804, the 5-year average production of antibiotics between 1971 and 1975 was 11.16 million pounds for medicinal uses and 7.68 million pounds for nonmedicinal uses, including feed additive uses. Over those 5 years, the aggregate average of the total production for those nonmedicinal uses was 40.8 percent—but 48.6 percent in 1975. Thus the use of antibiotics in animal feeds is a considerable element in the overall use of antibiotics in this country and consequently must be considered a significant contributor to the problem of R-plasmid antibiotic resistance. Penicillin and the tetracyclines are important among the antibiotics used in animal feeds.

Several methods of restricting the use of penicillin and tetracycline in animal feed, and thereby reducing the potential for harm associated with subtherapeutic antibiotic use, are available to the Commissioner. The most drastic method is to terminate their use completely in animal feed whether intended for therapeutic or subtherapeutic use, and this could perhaps be accomplished under the imminent hazard provision of section 512(e)(1) of the act. Another approach is to withdraw approval of all therapeutic and subtherapeutic uses that have not been shown to be safe or effective or that have available substitutes, and in the Commissioner's opinion, this is the most appropriate course of action at the present time. Accordingly, FDA has embarked on the latter course.

But a third supplementary method of controlling the use of these drugs is also available. The Commissioner can minimize the potential for harm associated with the widespread use of penicillin and tetracycline in animal feed by limiting their distribution through his authority to promulgate regulations under section 701(a) of the act (21 U.S.C. 371(a)) in conjunction with his substantive authority under sections 502(f), 512 (a), (b), (d), (i), and (m) (21 U.S.C. 352(f), 360b (a), (b), (d), (i), and (m)), to the order of a licensed veterinarian from feed mills holding approved medicated feed applications permitting the manufacture of such feed. The issues involved are generic, legally severable, and essentially policy; and such action also accomplishes the three functions that are identified in the Commissioner's April statement to the NAFDC. Moreover, that action is consistent with his earlier discussions in this area (see § 58.15(f)(1) (21 CFR 558.15(f)(1))) and all the recommendations from the independent groups advising the agency of this matter. For these reasons, the Commissioner is proposing such restrictions on the distribution of animal

feeds containing penicillin and tetracycline for comment although he is not foreclosing a reevaluation of the alternatives.

III. Scientific Basis for the Regulations

Soon after his discovery of penicillin, Sir Arthur Fleming noted that some bacterial organisms could become resistant to the antibiotic. As the use of antibiotics has increased, the numbers and types of bacterial resistance have also multiplied. There is a serious concern in the sceintific and medical communities that extensive, unnecessary exposure to antibiotics will lead to their declining usefulness in the treatment of both human and animal diseases. Currently, FDA is primarily concerned with that portion of increased antibiotic resistance in the ecological system which may result from the practice of feeding subtherapeutic levels of penicillin and tetracycline in animal feed for prolonged periods because this practice provides an ideal environment for selective pressure to operate. When exposed to an antibiotic, the organisms that are drug resistant survive while the growth of other (drug-sensitive) bacteria is inhibited. Eventually, the antibiotic resistant organisms predominate in the bacterial population, and continuous pressure perpetuates this abnormal situation.

Bacterial antibiotic resistance is primarily determined by genetic elements termed "R-plasmids" (R-factors, R+). The Commissioner's specific concern, therefore, is with the health hazard that may arise through an increase in the pool of R-plasmids in the animal population and the potential transfer of R-plasmid-bearing organisms from the animal to the human population and surrounding environment.

R-plasmids are small lengths of DNA that are separate from the bacterial chromosome. These R-plasmids carry transferable drug resistance genes as well as the capacity to reproduce themselves. Plasmids may determine resistance to more than one antibiotic, and resistance to several antibiotics is common. Moreover, plasmids can transfer from one bacteria to another and from nonpathogenic to pathogenic strains. Transfer occurs, although with varying frequency, between all members of the enteric bacteria and also the members of other families of bacteria. The pool of normal Gram-negative bacterial intestinal flora (largely *Escherichia coli*) serves as a reservoir of R-plasmids, and the R-plasmid-bearing bacteria interchange among animals, man, and the environment. The potential for harm increases as the R-plasmid reservoir increases because the probability of R-plasmid transfer to pathogens increases. When the Commissioner required all holders of approved NADA's for the subtherapeutic use of antibiotics (penicillin, tetracycline, etc.) in animal feed to submit data to resolve the safety questions raised, he was principally concerned with the effect of the antibiotics approved for subtherapeutic use in animal feed on the emergence of transferable drug resistance in *Salmonella* and the *E. coli* reservoir of animals.

Evidence demonstrates that the use of subtherapeutic levels of penicillin and tetracycline in animal feed contributes to the increase in antibiotic resistant *E. coli* and in the subsequent transfer of this resistance to *Salmonella*. Further, many strains of *E. coli* and *Salmonella* infect both man and animals.

There is extensive evidence showing that the use of subtherapeutic antibiotics contributes to the development of the pool of R-plasmid-bearing organisms, particularly in *E. coli* (Refs. *4* through *71*). These *E. coli* contribute their R-plasmids to man through several mechanisms: through man's direct contact with animals, through man's contact with *E. coli*-contaminated food, and through the widespread presence of plasmid-bearing *E. coli* in the environment (Refs. *8* through *38*). Various strains of bacteria inhabit and infect man and animals. The strains of bacteria that infect man and animals are not mutually exclusive; they overlap. In particular, the R-plasmid-bearing strains that colonize man and animals overlap. This has been shown by epidemiological investigations (Refs. *39* through *46*) and direct ingestion evidence (Refs. *47* through *51*). In vivo studies also show that the R-plasmids transfer from *E. coli* to pathogens, e.g., *Salmonella*, and that this actually occurs in humans (Refs. *52* through *68*). Of critical importance also is the fact that plasmid transfer occurs among nongut bacteria (Refs. *151-154*).

An agency study measuring the ability of R-plasmids to exist on the same bacterium suggests that human and animal bacterial populations overlap (Ref. *61*). Moreover, studies using DNA-DNA hybridization techniques and restriction endonuclease activity confirm that the R-plasmids isolated from enteric organisms in man and animals are indistinguishable (Refs. *62* through *64*). Studies also indicate that R-plasmid-bearing *E. coli* donate antibiotic resistance plasmids to *Salmonella*. Patterns of drug resistance seen in *E. coli* and *Salmonella* isolates from man and animals are similar and develop in a like manner. *E. coli* first develops R-plasmid-mediated antibiotic resistance, and then the *Salmonella* develop a similar and frequently identical pattern of resistance. Studies also show that the number of R-plasmid-bearing strains of pathogenic *Salmonella* are increasing. More importantly the number of multiply resistant strains is increasing (Refs. *65* through *124*).

According to the analysis of the Director of the Bureau of Veterinary Medicine, the evidence submitted pursuant to § 558.15 has failed to resolve the issues conclusively, and the potential for harm associated with the continued extensive use of subtherapeutic antibiotics in animal feeds continues to increase. Furthermore, evidence undermining the arguments that the unrestricted use of these products is safe continues to grow. For example, recent studies show that toxin production is plasmid mediated and may be transferred in conjunction with antibiotic resistance (Refs. *125* through *148*). All these points are set forth in considerably more detail in the Director's notices. Accordingly, the Commissioner concludes that transmissible drug resistance is a complex phenomenon with a potential for harmful effect that is not easily understood. Therefore, he finds that these drugs are not safe for use except under the order of a licensed veterinarian, to assure that the appropriate drugs are used for the shortest term possible or other measures are employed when for example, patent disease exists in the animals.

IV. Impact on the Medicated Feed Industry

The Director outlined his prima facie case in both the penicillin and tetracycline notices, and if unrebutted the Commissioner will issue an administrative summary judgment withdrawing approval of the NADA's for the affected drugs. If requests for hearing are filed that demonstrate that genuine and substantial issues of fact exist which require a formal evidentiary hearing for resolution, such a hearing will be granted to resolve those issues. But if a hearing is necessary, final resolution of the issues may take several years. Based on the evidence now before the Commissioner, he believes it appropriate at this point at least to propose to restrict the distribution and use of penicillin and tetracycline in animal feed. In his opinion, the evidence supports such action as a matter of policy, even if NADA holders demonstrate that approvals for the use of the drugs in animal feeds should not be withdrawn.

Issuing the proposal at this time accomplishes two objectives. First, although the Commissioner has previously considered the restrictive distribution alternative, this alternative has always been a minor element of the other proposals, and the Commissioner has never received focused comment on its feasibility and merit. Some contend that veterinarians lack the training, expertise, or willingness to deal with the potential for harm asso-

ciated with unbridled use of subtherapeutic antibiotics or pressures that may be applied to retain wide access to these drugs (Refs. *149, 150*).

Second, the Commissioner also would like comment on the potential impact that additional recordkeeping requirements will have on feed mills.

Finally, FDA has already issued FEDERAL REGISTER notices proposing to withdraw approval of the NADA's covering the subtherapeutic use of penicillin and tetracycline in animal feeds; therefore, the Commissioner has at least two options for selecting the effective date of regulations promulgated pursuant to this informal rulemaking procedure. The Commissioner can wait until the adjudications are concluded to issue a final order, or he can issue a final order before the adjudications are completed because this is a severable policy matter. If he should opt for the latter effective date, all approved uses of penicillin and tetracycline in animal feed then would be subject to the distribution restrictions in this regulation, and if any NADA's are ultimately withdrawn, corrections for the claims would be made with the final order in the adjudication proceedings. This approach will provide a stimulus for the expeditious conduct of any hearing that may be justified, and it will further reduce the imminence of any hazard that may exist. Accordingly, the Commissioner requests comments on the most appropriate effective date for this proposal.

V. LEGAL BASIS FOR THIS ACTION

As noted above, the Commissioner's authority to impose controls on the distribution of new animal drugs derives from several substantive sections of the act, sections 502(f)(1); 512 (a), (b), (d), (i), and (m), in conjunction with his rulemaking authority under section 701(a). In the aggregate they permit the Commissioner to restrict the distribution of new animal drugs and to require affected parties to keep certain records and reports on both drugs and medicated animal feeds that will permit the Commissioner to determine whether the continued use of the drugs under those circumstances is safe, effective, or otherwise appropriate.

A. STATUTORY AUTHORITY UNDER SECTION 502(f)(1)

Historically, FDA has restricted use of certain drugs in man and animals to the order of a practitioner under section 502(f)(1) of the act, which requires drug labeling to bear adequate directions for use, and an implementing exempting regulation. Under this approach, the labeling of certain drugs intended for human use was required to contain the statement: "Caution—To be used only by or on the prescription of a physician." Because of the dangers of incident to the use of certain drugs, only this warning could constitute adequate directions for use, and the Supreme Court has recognized this mechanism for restricting the use of drugs (*United States* v. *Sullivan*, 332 U.S. 689. 691, n.2 (1949)).

Subsequently, in a case decide before enactment of the Durham-Humphrey Amendment of 1951, the Ninth Circuit directly affirmed FDA's statutory authority to restrict the sale of a drug to the order of a licensed practitioner under section 502(f)(1) of the act and the companion implementing regulations:

> A liberal construction of the Act, having in mind its background and purposes, requires us to sustain the action of the Administrator on the ground that he was empowered under the statute to exempt the regulation the drugs in question from the requirement that the label bear adequate directions for use, conditioned upon its bearing an inscription that it be used only on the prescription of a physician. Under such construction, the regulation is not contrary to law, arbitrary, or unreasonable. (*United States* v. *El-O-Pathic Pharmacy*, 192 F. 2d 62, 75 (9th Cir. 1951).)

Although Congress enacted specific legislation that in part covers FDA authority to restrict the distribution of human drugs to a physician (Durham-Humphrey Amendment of 1951; 65 Stat. 648-649 (1951)), the legislative history of that amendment makes clear that Congress intended for FDA to retain this authority to restrict certain drugs to use according to a veterinarian's order under section 502(f)(1) of the act.

> In limiting prescription drugs to those intended for use by man this new subsection differs from the present law, which refers to prescription drugs to include not only those dispensed on prescription of physicians and dentists, but also those dispensed on prescription of a veterinarian. Under the committee bill, drugs intended for use under the supervision of a veterinarian will not require a prescription, although it will be possible under section 502(f) to exempt such drugs from adequate direction for use if they are to be used by or under the supervision of a veterinarian. In the absence of any exempting regulation, these drugs will be subject to the labeling and dispensing requirements of the act applicable to over-the-counter drugs. (S. Rep. No. 946, 82d Cong., 1st Sess., p. 8 (1951).)

The Commissioner promulgated such an exempting regulation for veterinary drugs under § 201.105 (21 CFR 201.105), and the regulation lays out the factors to be considered in assessing whether an animal drug should be restricted to a veterinarian's order. The factors are toxicity, potentiality for harmful effect, and the safety of the method of the drug's use. Thus, both the legislative history and case law demonstrate the Commissioner's authority to restrict the use of certain animal drugs to the order of a licensed veterinarian under the authority of section 502(f)(1) of the act, and the evidence surrounding the unrestricted use of penicillin and tetracycline in animal feed illustrates a potential for harm.

B. STATUTORY AUTHORITY UNDER SECTION 512 OF THE ACT

1. *Overview.* When Congress enacted the Animal Drug Amendments of 1968 and consolidated into section 512 the various provisions of the Federal Food, Drug, and Cosmetic Act governing the premarket approval of articles intended for use in animals and animal feeds, one primary force supporting the amendments was the medicated animal feed industry. (See, e.g., hearings on S. 1600 and H.R. 3639 before the Subcommittee on Health of the Senate Committee on Labor and Public Welfare, 90th Cong., 2d Sess. (1968).) Before passage of the amendments, articles intended for use in both food-producing and companion animals and in animal feed were subject to premarket review and clearance under sections 409, 505, and 507 of the act, and the consolidation incorporated the standards in those individual sections into section 512 (S. Rep. No. 1308, 90th Cong., 2d Sess. 1 (1968)).

Because new animal drugs are used extensively in food-producing animals, Congress imposed the same rigid legal standard on the intended uses of these articles that it applied to food additives. Therefore, when a new animal drug is intended for a use for which there is no approved NADA or the labeling of the new animal drug fails to conform to that in the approved NADA, the new animal drug is deemed unsafe as a matter of law (section 512(a)(1) of the act). The new animal drug is thereby adulterated per se under section 501(a)(5) of the act (21 U.S.C. 351(a)(5)), and food containing the new animal drug or conversion product thereof is also adulterated as a matter of law under section 402(a)(2)(D) of the act (21 U.S.C. 342(a)(2)(D)). Similarly, animal feed containing a new animal drug is unsafe as a matter of law under section 512(a)(2) unless the following conditions are satisfied: (a) There is an approved NADA for that specific use of the drug in animal feed; (b) there is an approved medicated feed application (FD Form 1800) under section 512(m)(1) for that use; and (c) the animal feed, its labeling, and use conform with a regulation issued under section 512(i). A medicated animal feed which does not conform with these requirements is adulterated under section 501(a)(6) of the act.

2. *Sections 512 (b) and (d).* The statutory criteria that FDA must use to evaluate the safety and effectiveness of new animal drugs are set forth in sections 512 (b) and (d) of the act and the corresponding amplifying regula-

tions under Parts 500 and 514 (21 CFR Parts 500 and 514). Unlike section 505 of the act, which covers new human drugs, section 512(d)(2) enumerates several specific factors that are to be considered by the agency in determining whether a new animal drug will be safe under its proposed conditions of use. The factors, which were taken directly from considerations associated with the safety of human food additives under section 409(c)(5) of the act, are the following:

(A) The probable consumption of such drug and of any substance formed in or on food because of the use of such drug,

(B) The cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance,

(C) Safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data, and

(D) Whether the conditions of use prescribed recommended, or suggested in the proposed labelling are reasonably certain to be followed in practice.

Thus, these provisions clearly envision the exercise of FDA's authority to impose restrictions on the distribution and use of new animal drugs, particularly when the drug is intended for use in food-producing animals.

3. *Section 512(i).* Section 512(i) of the act requires FDA to publish a notice of approval for every NADA, which becomes effective as a regulation upon publication in the FEDERAL REGISTER. The function of the new animal drug regulations under this provision is analogous to the function of food additive regulations issued under section 409 of the act (hearings on S. 1600 and H.R. 3639 supra at 80; S. Rep. No. 1308 supra at 5). They are to provide public notice, particularly to manufacturers of medicated animal feeds, of the conditions and restrictions of use that are imposed on the new animal drugs. But the new animal drug regulations provide more than general notice. Section 512(i) identifies several factors that are to be addressed in the regulations in order to assure that a new animal drug will be properly used in the field. Among these factors are the specific conditions of use under which the drug has been shown to be safe and effective, any other use restriction imposed, and such other information as the agency deems necessary to assure the safe and effective use of the new animal drug. Therefore, Congress provided FDA with another statutory provision by which it can restrict the distribution of a new animal drug.

4. *Section 512(m).* Subsection (m) of section 512 of the act presents a microcosm of the entire section. Basically, this provision was added to simplify the procedural and substantive requirements of the act as they pertain to medicated feed mills. It establishes a private licensing section for feed mills to manufacture medicated animal feeds which is substantially similar to the NADA review and approval procedures. As a condition of having the license (in this case a medicated feed application) approved, the feed mill must identify a new animal drug regulation providing for the manufacture and use of the new animal drug under the conditions or indications of use for which the mill proposes to manufacture the medicated feed.

Section 512(m)(1) of the act outlines the basic information that a feed mill must submit to FDA to obtain an approved medicated feed application for a specific medicated animal feed, and section 512(m)(3) lists the bases on which the agency can refuse to approve the application. The agency shall refuse to approve an application when it finds among other facts:

(A) That there is not in effect a regulation under subsection (i) (identified in such application) on the basis of which such application may be approved;

(B) That such animal feed (including the proposed use of any new animal drug therein or thereon) does not conform to an applicable regulation published pursuant to subsection (i) referred to in the application, or that the purposes and conditions or indications of use prescribed, recommended, or suggested in the labeling of such feed do not conform to the applicable purposes and conditions or indications of use (including warnings) published pursuant to subsection (i) or such labeling omits or fails to conform to other applicable information published pursuant to subsection (i).

Section 512(m) of the act also contains a provision for recordkeeping requirements on the feed mills, and this provision is identical to that applicable to the manufacturers of new animal drugs (sections 512(d)(2)(A); 512(1)). In addition to the normal records required by good manufacturing practice, etc., the manufacturers of medicated animal feeds must keep all records and make all such reports that the Commissioner imposes on them by general regulation when those records and reports are necessary to determine or facilitate a determination of whether the medicated animal feed may be safely, effectively, or otherwise appropriately used. And these records and reports must be available to FDA for inspection.

C. STATUTORY AUTHORITY UNDER SECTION 701(A) OF THE ACT

The agency's authority to promulgate substantive regulations under section 701(a) defining and explaining the operative provisions of the act and applying those provisions to particular classes of products has been consistently, if not uniformly, upheld by the courts, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688 (2d Cir. 1974). (See also In re *Permain Basin Rate Cases*, 390 U.S. 766 (1968); *Federal Power Commission* v. *Texaco, Inc.* 377 U.S. 33 (1964); *Air Lines Pilots Association, International* v. *Quesada*, 276 F. 2d 892 (2d Cir. 1960).) Moreover, FDA's authority to determine whether a new animal drug has been shown to be safe and effective under the restrictive distribution system of a veterinarian's order is well established (*Diamond Laboratories, Inc.* v. *Richardson*, 452 F. 2d 803 (8th Cir. 1972)), as has its authority to restrict the use of a new animal drug to only those conditions of use that have been shown to be safe and effective (*Agri-Tech, Inc.* v. *Richardson*, 482 F. 2d 1148 (8th Cir. 1973)).

D. CONCLUSION

The agency regularly imposes distribution requirements on new animal drugs pursuant to Parts 520 through 555 (21 CFR Parts 520 through 555). Given the evidence on the unrestricted use of penicillin and tetracycline in animal feed, the Commissioner believes there is ample statutory authority for him to promulgate regulations restricting all uses of penicillin and tetracycline in animal feed to the order of a veterinarian, which order must be retained by the holder of an approved medicated feed application permitting manufacture of the feed or by other persons subsequently dispensing restricted feed obtained from the holder of the application.

VI. SUMMARY OF THE PROPOSAL

To implement this action, the Commissioner is proposing to amend the regulations to establish a new medicated animal feed category called restricted medicated animal feeds, which will require an approved medicated feed application for manufacture and for distribution on the order of a licensed veterinarian. This category will include, with two minor exceptions, all feeds containing penicillin, chlortetracycline, and oxytetracycline. Accordingly, he is proposing to revoke all existing waivers from the requirements of section 512(m) of the act for the manufacture of such animal feeds, and the manufacture of these animal feeds will then require an approved medicated feed application. Because veterinarians may require a form of the drug for immediate dispensing (i.e., either directly by a veterinarian or by a feed mill on the order of a licensed veterinarian) in their practices to deal with exigencies, the Commissioner is proposing an exemption from the requirements of section 512(m) for the manufacture of restricted animal feeds from a restricted article containing 2 grams per pound of the antibiotics penicillin, chlortetracycline, or oxytetracycline as the sole drug in medicated feed in 50-pound packages. He selected this

size for its convenience for dispensing and for use by livestock producers.

Proposed § 558.7(a) (21 CFR 558.7(a)) defines animal feeds containing penicillin or chlortetracycline (except feeds for laboratory mice and psittacine birds) or oxytetracycline as restricted medicated animal feeds. The Commissioner has excluded the uses of chlortetracycline in feeds for laboratory mice and psittacine birds from the restricted category because of the limited and special nature of those uses.

Proposed § 558.7(b)(1) establishes the basic requirement for the manufacturers of restricted medicated animal feeds. Under this provision, all feed mills will require an approved medicated feed application for each restricted medicated animal feed they produce. This section also contains the exemption for the manufacture of a restricted medicated animal feed under the order of a licensed veterinarian. The exemption applies only when such feed is prepared from a concentrated restricted medicated animal feed which contains 2 grams per pound of penicillin, chlortetracycline, or oxytetracycline as the sole drug in medicated feed in 50-pound packages. This permits the veterinarian to deal with urgent situations by dispensing a concentrated medicated feed directly to the livestock producer who will be able to mix a complete feed without having an approved medicated feed application. The Commissioner will permit manufacturers 60 days from the date of publication of a final order based upon this approval to submit a medicated feed application.

Proposed § 558.7(b)(2) requires the manufacturers of intermediate premixes (proposed Type B medicated feed articles) containing penicillin, chlortetyracycline, or oxytetracycline to have approved medicated feed applications for the manufacture of these products. Currently manufacturers of these intermediate premixes are exempt, under § 558.15(g) (21 CFR 558.15(g)), from having an approved NADA if the intermediate premix contains no drug ingredient whose use in or on an animal feed requires an approved medicated feed application. Since the Commissioner is proposing to revoke this exemption for the manufacture of medicated feeds containing penicillin, chlortetracycline, or oxytetracycline, codifying this requirement will simplify regulation of this area.

Ostensibly, revocation of the exemption would also require manufacturers of intermediate premixes to have approved new animal drug applications for their products. However, the Commissioner intends to issue a proposal in the near future to regulate the intermediate premixes as Type B medicated feed articles under sections 201(x) and 512(m) of the act (21 U.S.C. 321(x) and 360b(m)), for administrative and regulatory efficiency. For these reasons, the Commissioner is now proposing to regulate intermediate premixes for the restricted medicated animal feeds also under section 512(m) of the act for consistency. This will permit an orderly transition to more extensive regulation via medicated feed applications. The Commissioner will permit manufacturers of the restricted feeds 60 days from the date of publication of the final order in this procedure to submit a medicated feed application for these medicated feed articles. If these provisions are placed into effect prior to completion of the adjudication concerning penicillin and tetracycline premixes, manufacturers of intermeidate premixes (or Type B medicated feed articles) may identify the appropriate provision of § 558.15 as the basis for approving their medicated feed application for those uses which have been permitted interim marketing and for which a regulation under section 512(i) of the act has not been published.

Proposed § 558.7(c)(1) requires restricted medicated animal feeds to be dispensed only if accompanied by and in accordance with the order of a licensed veterinarian. Although restricted medicated animal feeds containing 2 grams of penicillin, chlortetracycline, or oxytetracycline as the sole drug in 50-pound packages may be sold to licensed veterinarians for dispensing purposes in their practices, the feed mills must retain records for these transactions also.

Proposed § 558.7(c)(2) describes the recordkeeping requirements. The veterinarian's order must be either a signed written order or an oral order given directly to the party who is to dispense the restricted medicated animal feed and such order must be promptly reduced to writing. The order shall include the following information:

1. Veterinarian's name, address, and telephone number;
2. Client's name and address;
3. Type of feed (e.g., starter, grower, finishing ration), including the quantitative level of the drug(s) involved (e.g. grams per ton).
4. Species to be treated, and indications for use;
5. Total amount of feed to be mixed and number of refills permitted. The amount of feed prescribed shall not exceed the amount reasonably necessary to treat the number of animals involved; and
6. Date.

The records must be retained at the point of sale by the dispensing party for a period not less than 2 years because the agency has a statutory obligation to inspect every feed mill at least once every 2 years. This requirement is also applicable to integrated livestock producers who have approved medicated feed applications for restricted medicated animal feeds and who manufacture such feeds for their own use.

Proposed § 558.7(d) explains how FDA will regulate feed stores or other distributors of medicated animal feeds that may be restricted. These segments of the medicated animal feed industry are essentially consignees who are not the users of the articles. Under section 512(a)(1) of the act, consignors may ship new animal drugs to such consignees if they are holders of approved medicated feed applications or, if the consignees are not users, to such consignees that will ship only to holders of approved medicated feed applications. Because the mechanism of distribution by the feed stores is merely a further step in the chain, the Commissioner is proposing to permit holders of approved applications for restricted medicated animal feeds to dispense those feeds to feed stores and other distributors on the condition that those consignees supply the feed mill with a signed statement indicating that they will dispense restricted medicated animal feeds on and in accordance with the order of a licensed veterinarian, that they will maintain the required records of such dispensing for at least 2 years, and that they will permit inspection of the records at all reasonable hours by any duly authorized officer or employee of FDA or other employee acting on behalf of the Secretary of HEW. This will permit a distributor, who does not have approved medicated feed applications under section 512(m) of the act, to receive restricted medicated animal feeds and to dispense them in accord with the rationale for the regulation. Failure of holders of approved applications to comply with these requirements will result in the Commissioner's proposing to withdraw approval of the feed mill's medicated feed application for the restricted feed and to take any other appropriate legal action that is warranted.

Proposed § 558.7(e) sets forth specific label and labeling requirements for (1) articles that are to be manufactured into restricted medicated animal feeds and (2) restricted medicated animal feeds, in addition to all the other labeling requirements of the act. Articles that are to be further manufactured into restricted feed must bear the statement: "For use only in the manufacture of restricted medicated animal feeds to be used on the order of a licensed veterinarian".

For complete restricted medicated animal feeds, the label and labeling shall bear the statement "For use only on the order of a licensed veterinarian".

Proposed § 558.7(e)(3) requires that all restricted medicated animal feeds

dispensed on the order of a licensed veterinarian be appropriately labeled for use and that such use shall include only those conditions for which the article has been approved under Part 558.

Proposed § 558.7(f) provides that an animal feed which contains two or more animal drugs is a restricted medicated animal feed if any ingredient alone would cause a feed containing it to be a restricted medicated animal feed.

Finally, proposed § 558.7(g) establishes the implementation plan. A veterinarian's order will be required for the dispensing of any restricted medicated animal feed 150 days after publication of a final regulation based upon this proposal. This will permit an orderly transition period for processing medicated feed applications that form the bases for this proposal.

The Commissioner has carefully considered the environmental effects of this action, and he has concluded that an environmental impact statement is not required for this notice. A copy of the environmental impact assessment is on file with the Hearing Clerk. Moreover, in the FEDERAL REGISTER of May 27, 1977 (42 FR 27264), the Commissioner of Food and Drugs requested data concerning the potential environmental impact of a series of regulatory actions, including this one, designed to restrict the subtherapeutic use of antibacterials in animal feeds. A comprehensive environmental impact statement will be prepared, evaluating the impact of all the actions as a single program.

REFERENCES

1. Report of the Antibiotics in Animal Feeds Subcommittee of the National Advisory Food and Drug Committee on the Subtherapeutic Use of Antibiotics in Animal Feed.

2. Transcript of the January 24, 1977 Meeting of the National Advisory Food and Drug Committee.

3. Statement of Donald Kennedy, Commissioner of Food and Drugs, to National Advisory Food and Drug Committee, April 15, 1977.

4. Mercer, H. D., D. Pocurul, S. Gaines, S. Wilson, and J. V. Bennett, "Characteristics of Antimicrobial Resistance of *Escherichia coli* from Animals: Relationship to Veterinary and Management Uses of Antimicrobial Agents," Applied Microbiology, 22:700–705, 1971.

5. Seigel, D., W. G. Huber, and F. Enloe, "Continuous Nontherapeutic Use of Antibacterial Drugs in Feed and Drug Resistance of the Gram-negative Enteric Flora of Food-Producing Animals," Antimicrobial Agents and Chemotherapy, 6:697–701, 1974.

6. Smith, H. W., and J. F. Tucker, "The Effect of Antibiotic Therapy on the Faecal Excretion of *Salmonella typhimurium* by Experimentally Infected Chickens," Journal of Hygiene, 75:275–292, 1975.

7. Katz, S. E., C. A. Fassbender, P. S. Dinnerstein, and J. J. Dowling, Jr., "Effects of Feeding Penicillin to Chickens," Journal of the Association of Official Analytical Chemists, 57:522–526, 1974.

8. Linton, K. B., P. A. Lee, M. H. Richmond, W. A. Gillespie, J. J. Rowland, and V. N. Baker, "Antibiotic Resistance and Transmissible R-factors in the Intestinal Coliform Flora of Healthy Adults and Children in an Urban and Rural Community," Journal of Hygiene, 70:99–104, 1972.

9. Wells, D. M., and O. B. James, "Transmission of Infectious Drug Resistance from Animals to Man," Journal of Hygiene, 71:209–215, 1973,

10. Siegel, D., W. G. Huber, and S. Drysdale, "Human Therapeutic and Agricultural Uses of Antibacterial Drugs and Resistance of the Enteric Flora of Humans," Antimicrobial Agents and Chemotherapy, 8:538–543, 1975.

11. Levy, S. B., G. B. Fitzgerald, and B. S. Macone, "Change in Intestinal Flora of Farm Personnel After Introduction of a Tetracycline-Supplemented Feed on a Farm," New England Journal of Medicine, 295:583–588, 1976.

12. Levy, S. B., G. B. Fitzgerald, and A. B. Macone, "Spread of Antibiotic Resistant Plasmids From Chicken to Chicken and from Chicken to Man," Nature, 260:40–42, 1976.

13. Howe, K., and A. H. Linton, "The Distribution of O-Antigen Types of *Escherichia coli* in Normal Calves, Compared with Man, and Their R-plasmid Carriage," Journal of Applied Bacteriology, 40:317–330, 1976.

14. Anderson, E. S., "The Ecology of Transferable Drug Resistance in the Enterobacteria," Annual Review of Microbiology, 22:131–180, 1968.

15. Howe, K., A. H. Linton, and A. D. Osborne, "A Longitudinal Study of *Escherichia coli* in Cows and Calves with Special Reference to the Distribution of O-Antigen and Antibiotic Resistance," Journal of Applied Bacteriology, 40:331–340, 1976.

16. Loken, K. I., L. W. Wagner, and C. L. Henke, "Transmissible Drug Resistance in Enterobacteriaceae Isolated From Calves Given Antibiotics," American Journal of Veterinary Research, 32:1207–1212, 1971.

17. Mercer, H. D., D. Pocurull, S. Gaines, S. Wilson, and J. V. Bennett, "Characteristics of Antimicrobial Resistance of *Escherichia coli* from Animals: Relationship to Veterinary and Management Uses of Antimicrobial Agents," Applied Microbiology, 22:700–705, 1971.

18. Smith H. W., "The Effect of the Use of Antibacterial Drugs, Particularly as Food Additives, on the Emergence of Drug Resistant Strains of Bacteria in Animals," New Zealand Veterinary Journal, 15:153–166, 1967.

19. Smith, H. W., "The Effect of the Use of Antibacterial Drugs on the Emergence of Drug-Resistant Bacteria in Animals," Advances in Veterinary Science and Comparative Medicine, 15:67–100, 1971.

20. Smith, H. W., and W. E. Crabb, "The Effect of the Continuous Administration of Diets Containing Low Levels of Tetracyclines on the Incidence of Drug-Resistant *Bacterium coli* in the Faeces of Pigs and Chickens: The Sensitivity of *Bact. coli* to Other Chemotherapeutic Agents," Veterinary Record, 69:24–30, 1957.

21. Walton, J. R., "Contamination of Meat Carcasses by Antibiotic-Resistant Coliform Bacteria," Lancet, 2:561–563, 1970.

22. Walton, J. R., and L. E. Lewis, "Contamination of Fresh and Cooked Meats by Antibiotic Resistant Coliform Bacteria," Lancet, 2:255, 1971.

23. Babcock, G. F., D. L. Berryhill, and D. H. Marsh, "R-Factors of *Escherichia coli* from Dressed Beef and Humans," Applied Microbiology, 25:21–23, 1973.

24. Kim, T. K., and J. F. Stephens, "Drug Resistance and Transferable Drug Resistance of *E. coli* Isolated from 'Ready-to-Cook' Broilers," Poultry Science, 51:1165–1170, 1972.

25. Shooter, R. A., E. M. Cooke, S. O'Farrell, K. A. Bettelheim, M. E. Chandler, and F. M. Bushrod, "The Isolation of *Escherichia coli* from a Poultry Packing Station and an Abattoir," Journal of Hygiene, 73:245–247, 1974.

26. Cooke, E. M., A. L. Braeden, R. A. Shooter, and S. M. O'Farrell, "Antibiotic Sensitivity of *Escherichia coli* Isolated from Animals, Food, Hospital Patients, and Normal People," Lancet, 2:8–10, 1971.

27. Howe, K., A. H. Linton, and A. D. Osborne, "An Investigation of Calf Carcass Contamination from *Escherichia coli* from the Gut Contents at Slaughter," Journal of Applied Bacteriology, 41:37–45, 1976.

28. Linton, A. H., B. Handley, A. D. Osborne, B. G. Shaw, T. A. Roberts, and W. R. Hudson, "Contamination of Pig Carcasses at Two Abattoirs by *Escherichia coli* with Special Reference to O-Serotypes and Antibiotic Resistance," Journal of Applied Bacteriology, 42:89–111, 1977.

29. Linton, A. H., K. Howe, C. L. Hartley, and H. M. Clements, "Antibiotic Resistant and Sensitive *Escherichia coli* O-serotypes in the Gut and on the Carcass by Commercially Slaughtered Broiler Chickens and the Potential Public Health Implications," in press 1977.

30. Shooter, R. A., S. A. Rousseau, E. M. Cooke, and A. L. Braeden, "Animal Sources of Common Serotypes of *Escherichia coli* in the Food of Hospital Patients," Lancet, 2:226–228. 1970.

31. FDC Docket No. 77N–0156, Environmental Impact Analysis and Assessment Reports (EIAR/EAR) for Chlortetracycline-Penicillin-Sulfonamides (CSP) and Penicillin Streptomycin Premix Combinations.

32. Cooke, M. D., "Antibiotic Resistance among Coliform and Fecal Coliform Bacteria Isolated from Sewage, Seawater, and Marine Shallfish," Antimicrobial Agents and Chemotherapy, 9:879–884, 1976.

33. Feary, R. W., A. B. Sturvetant, and J. Lankford, "Antibiotic-Resistant Coliforms in Fresh and Salt Water," Archives of Environmental Health, 25:215–220, 1972.

34. Grabow, W. O. K., and O. W. Prezesky, "Drug Resistance of Coliform Bacteria in Hospital and City Sewage," Antimicrobial Agents and Chemotherapy, 3:175–180, 1973.

35. Linton, K. B., M. H. Richmond, R. Bevan, and W. A. Gillespie, "Antibiotic Resistance and R Factors in Coliform Bacilli Isolated from Hospital and Domestic Sewage," Journal of Medical Microbiology, 7:91–103, 1974.

36. Richmond, M. H., "R Factors in Man and His Environment," in "Microbiology—1974," edited by D. Schlessinger, American Society for Microbiology, Washington, D.C. 1975.

37. Smith, H. W., "Incidence in River Water of *Escherichia coli* Containing R-Factors," Nature, 228:1280–1286, 1970.

38. FDC Docket No. 77–0156, EIAR for CSP.

39. Bettelheim, K. A., A. M. Bushrod, E. Chandler, E. M. Cooke, S. O'Farrell, and R. A. Shooter, "*Escherichia coli* Serotype Distribution in Man and Animals," Journal of Hygiene, 73:467–471, 1974.

40. Bettelheim, K. A., N. Ismail, R. Shinebaum, R. A. Shooter, E. Moorhouse, and

Wendy Farrell, "The Distribution of Serotypes of *Escherichia coli* in Cow-Pats and Other Animal Material Compared with Serotypes of *E. coli* Isolated from Human Sources," Journal of Hygiene, 76:403-406, 1976.

41. Hartley, C. L., K. Howe, A. H. Linton, K. B. Linton, and M. H. Richmond, "Distribution of R-Plasmids Among the O-Antigen Types of *Escherichia coli* Isolated from Human and Animal Sources," antimicrobial Agents and Chemotherapy, 8:122-131, 1975.

42. Howe, K., and A. H. Linton, "The Distribution of O-Antigen Types of *Escherichia coli* in Normal Calves, Compared with Man, and Their R-Plasmid Carriage," Journal of Applied Bacteriology, 40:317-330, 1976.

43. Howe, K., A. H. Linton, and A. D. Osborne, "A Longitudinal Study of *Escherichia coli* in Cows and Calves with Special Reference to the Distribution of O-Antigen and Antibiotic Resistance," Journal of Applied Bacteriology, 40:331-340, 1976.

44. Linton, A. H., B. Handley, A. D. Osborne, B. G. Shaw, T. A. Roberts, and W. R. Hudson, "Contamination of Pig Carcasses at Two Abattoirs by *Escherichia coli* with Special Reference to O-Serotypes and Antibiotic Resistance," Journal of Applied Bacteriology, 42:89-111, 1977.

45. Petrocheilou, V., and M. H. Richmond, "Distribution of R-Plasmids Among the O-Antigen Types of *Escherichia coli* Isolated from Various Clinical Sources," Antimicrobial Agents and Chemotherapy, 9:1-5, 1976.

46. Howe, K., A. H. Linton, and A. D. Osborne, "The Effect of Tetracycline on the Coliform Gut Flora of Brioler Chickens with Special Reference to Antibiotic Resistance and O-Serotypes of *Escherichia coli*," Journal of Applied Bacteriology, 41:453-464, 1976.

47. Smith, H. W., "Transfer of Antibiotic Resistance from Farm Animals and Human Strains of *Escherichia coli* to Resident *E. coli* in the Alimentary Tract in Man," Lancet, 1:1174-1176, 1969.

48. Cooke, E. M., I. G. T. Hetiarchy, and C. A. Buck, "Fate of Ingested *Escherichia coli* in Normal Persons," Journal of Medical Microbiology, 5:361-369, 1972.

49. Anderson, J. D., W. A. Gillespie and M. H. Richmond, "Chemotherapy and Antibiotic-Resistance Transfer between Enterobacteria in the Human Gastro-intestinal Tract," Journal of Medical Microbiology, 6:461-473, 1973.

50. Anderson, J. D., L. C. Ingram, M. H. Richmond, and B. Wiedemann, "Studies on the Nature of Plasmids Arising from Conjugation in the Human Gastro-intestinal Tract," Journal of Medical Microbiology, 6:475-486, 1973.

51. Linton, A. H., K. Howe, P. M. Bennett, M. H. Richmond, and E. J. Whiteside, "The Colonization of the Human Gut by Antibiotic Resistant *Escherichia coli* from Chickens," in press, 1977.

52. Anderson, J. D., W. A. Gillespie and M. H. Richmond, "Chemotherapy and Antibiotic-Resistance Transfer between Enterobacteria in the Human Gastro-intestinal Tract," Journal of Medical Microbiology, 6:461-473, 1973.

53. Guinee, P. M., "Transfer of Multiple Drug Resistance from *Escherichia coli* to *Salmonella typhimurium* in the Mouse Intestine," Antonie van Leeuwenhoek; Journal of Microbiology and Serology, 31:314-322, 1965.

54. Kasuya, M., "Transfer of Drug Resistance between Enteric Bacteria Induced in the Mouse Intestine," Journal of Bacteriology, 88:322-331, 1964.

55. Nivas, S. C., M. D. York, and B. S. Pomeroy, "In Vitro and In Vivo Transfer of Drug Resistance from *Salmonella* and *Escherichia coli* Strains in Turkeys," American Journal of Veterinary Research, 37:433-437, 1976.

56. Salzman, T. C., and L. Klemm, "Transfer of Antibiotic Resistance (R-factor) in the Mouse Intestine," Proceedings of the Society of Experimental and Biological Medicine, 28:392-394, 1968.

57. Smith, H. W., "Transfer of Antibiotic Resistance from Farm Animals and Human Strains of *Escherichia coli* to Resident *E. coli* in the Alimentary Tract in Man," Lancet, 1:1174-1176, 1969.

58. Smith, H. W., "The Transfer of Antibiotic Resistance between Strains of Enterobacteria in Chickens, Calves, and Pigs," Journal of Medical Microbiology, 3:165-180, 1970a.

59. Walton, J. R., "In Vivo Transfer of Infective Drug Resistance," Nature, 211:312-313, 1966.

60. Smith, H. W., and J. F. Tucker, "The Effect of Antibiotic Therapy on the Faecal Excretion of *Salmonella typhimurium* by Exprimentally Infected Chickens," Journal of Hygiene, 75:275-292, 1975.

61. FDA contract 223-73-7210.

62. Anderson, E. S., G. O. Humphreys, and G. A. Willshaw, "The Molecular Relatedness of R-factors in Enterobacteria of Human and Animal Origin," Journal of General Microbiology, 91:376-382, 1975.

63. Grindlay, N. D. F., G. O. Humphreys, and E. S. Anderson, "Molecular Study of R-factor Compatibility Groups," Journal of Bacteriology, 115:387-398, 1973.

64. Crosa, J., J. Olarte, L. Matry, L. Luttropp, and M. Penaranda, "Characterization of an R-Plasmid Associated with Ampicillin Resistance in *Shigella Dysenteriae* Type 1 Isolated from Epidemics," Antimicrobial Agents and Chemotherapy, 11:553-558.

65. Williams, R., L. Rollins, M. Selwyn, D. Pocurull, and H. D. Mercer, "The Effect of Feeding Chlortetracycline on the Fecal Shedding of *Salmonella typhimurium* by Experimentally Infected Swine," submitted to Antimicrobial Agents and Chemotherapy, in "Proceedings of Antibiotics in Animal Feeds Subcommittee," April 27-28, 1976.

66. Walton, J., "In Vivo Transfer of Drug Infective Resistance," Nature, 211:312-313, 1966.

67. Neu, H. C., et al., "Antimicrobial Resistance and R-Factor Transfer Among Isolates of *Salmonella* in the Northeastern United States: A Comparison of Human and Animal Isolates," Journal of Infectious Diseases, 132:617-622, 1975.

68. Gill, F. A., E. W. Hook, "*Salmonella* Strains with Transferable Antimicrobial Resistance," Journal of the American Medical Association, 198:129-131, 1966.

69. CDC Personal Communications from R. Ryder, June 18, 1971 and Personal Communication from J. Bennett, July 26, 1977.

70. Schroeder, S. A., P. M. Terry, and J. V. Bennett, "Antibiotic Resistance and Transfer Factor in *Salmonella*, United States 1967," Journal of the American Medical Association, 205:87-90, 1968.

71. Bennett, J., Testimony before the Subcommittee on Oversight and Investigation of the House Committee on Interstate and Foreign Commerce, September 23, 1977.

72. Langworth, B. and H. Jarolmen, "Antibiotic Defense: Transferable Drug Resistance of Clinical Bacterial Isolates from a Hospital in an Agricultural and in One Non-agricultural Area," Project 3-733, NADA 48-761, Exhibit 8, submitted to FDA, May 20, 1975.

73. Royal, W., R. Robinson, R. Hunter, H. MacDiarmid, "Multiple Drug Resistance," New Zealand Veterinary Journal, 16:20, 1967.

74. Marsik, F., J. T. Parisi, et al., "Transmissible Drug Resistance of *E. coli* and *Salmonella* from Humans, Animals and Their Rural Environments," Journal of Infectious Diseases, 132:296-302, 1975.

75. Manten, A., P. A. M. Guinee, E. H. Kampelmacher, and C. E. Voogd, "An Eleven-Year Study of Drug Resistance in *Salmonella* in the Netherlands," (Bull. Or. Mond. Sante.) World Health Organization Bulletin, 45:85-93, 1971.

76. Pocurull, D. W., S. A. Gaines, and H. D. Mercer, "Survey of Infectious Multiple Drug Resistance *Salmonella* Isolated from Animals in the United States," Applied Microbiology, 21:358-362, 1971.

77. Ramsey, C. H., and P. R. Edwards, "Resistance of *Salmonellae* Isolated in 1959 and 1960 to Tetracyclines and Chloramphenicol," Applied Microbiology, 9:389-391, 1961.

78. McWhorter, A. C., M. C. Murrey and P. R. Edwards, "Resistance of *Salmonellae* Isolated in 1962 to Chlortetracycline," Applied Microbiology, 11:368-370, 1963.

79. Kaye, D., J. C. Merselis, Jr., and E. W. Hook, "Susceptibility of *Salmonella* Species to Four Antibiotics," New England Journal of Medicine, 269:1084-1086, 1963.

80. Winshell, E. B., C. Cherubin, J. winter, and H. C. Neu, "Antibiotic Resistance of *Salmonella* in the Eastern United States," Antimicrobial Agents and Chemotherapy, 9:86-89, 1969.

81. Cherubin, C. E., M. Szmuness, and J. Winter, "Antibiotic Resistance of *Salmonella* Northeastern United States—1970," New York State Journal of Medicine, 130:369-372, 1972.

82. Bissett, M. J., S. L. Abbott, and R. M. Wood, "Antimicrobial Resistance and R-Factors in *Salmonella* Isolated in California, 1971-1972," Antimicrobial Agents and Chemotherapy, 5:161-168, 1974.

83. Reid, B. L., J. F. Elam, J. R. Couch, et al., "The Effect of Oral and Parenteral Administration of Antibiotics on Growth and Fecal Microflora in the Turkey Poult," Poultry Science, 33:307-309, 1954.

84. Smith, H. W. and W. E. Crabb, "The Effect of the Continuous Administration of Diets Containing Low Levels of Tetracyclines on the Incidence of Drug-resistant *Bacterium coli* on the Faeces of Pigs and Chickens: The Sensitivity of the *Bacterium coli* to Other Chemotherapeutic Agents," Veterinary Record, 69:24-30, 1957.

85. Gordon, R., J. S. Garside and J. Tucker, "Emergence of Resistant Strains of Bacteria Following the Continuous Feeding of Antibiotics to Poultry," Proc. XVIth Int. Vet. Congress. Madrid, 2:347, 1959.

86. Harry, E. G., "The Ability of Low Concentrations of Chemotherapeutic Substances to Induce Resistance in *E. coli*," Poultry science, 3:85-93, 1964.

87. Levy, S., G. Fitzgerald, A. Macone, "Changes in Intestinal Flora of Farm Personnel after Introduction of a Tetracycline Supplemented Feed on a Farm," New England Journal of Medicine, 295:553-588, 1976.

88. Levy, S. B., G. B. Fitzgerald, A. B. Macone, "Spread of Antibiotic Resistant Plasmids from Chicken to Chicken and from Chicken to Man," Letter to Nature, 260:40-42, 1976.

89. Smith, H., and J. F. Tucker, "The Effect of Antibiotic Therapy on the Faecal

Excretion of *Salmonella typhimurium* by Experimentally Infected Chickens," Journal of Hygiene, 75:275-292, 1975.

90. MacKenzie, M. M., and B. S. Baines, "The Effect of Antibacterials on Experimentally Induced *Salmonella typhimurium* Infection in Chickens," Poultry Science, 53:307-310, 1974.

91. Rantala, M., "Nitrovin and Tetracycline: A Comparison of Their Effect on Salmonellosis in Chicks," British Poultry Science, 15:299-303, 1974.

92. Garside, J. S., R. F. Gordon, and J. F. Tucker, "The Emergence of Resistant Strains of *Salmonella typhimurium* in the Tissues and Alimentary Tracts of Chickens following the Feeding of an Antibiotic," Research in Veterinary Science, 1:184-199, 1960.

93. Hobbs, B. et al., "Antibiotic Treatment of Poultry in Relations to *S. typhimurium*," Month. Bull. Ministry Health, G. B., 19:178-192, 1960.

94. Siegel, D., "The Ecological Effects of Antimicrobial Agents on Enteric Florae of Animals and Man," Final Technical Report FDA Contact 71-269, University of Illinois, College of Veterinary Medicine, 1976.

95. Mercer, H. D., D. Pocurull, S. Gaines, S. Wilson, and J. O. Bennett, "Characteristics of Antimicrobial Resistance of *Escherichia coli* from Animals. Relationships to Veterinary and Management Uses of Antimicrobial Agents," Applied Microbiology, 22:4:700-705, 1971.

96. McKay, K. A. and H. D. Branion, "The Development of Resistance to Terramycin by Intestinal Bacteria of Swine," Canadian Veterinary Journal, 1:144-149, 1960.

97. Langlois, B., G. Cromwell, V. Hays, "Influence of Antibacterial Agents in Feed on the Incidence and Persistence of Antibiotic-Resistant Members of the Family Enterobacteriaceae *E. coli* Isolated From Swine," Final report to Animal Health Institute, submitted to FDA April 14, 1976.

98. Farrington and Switzer, "Determination of the Ratio of Antibiotic-Resistant Coliforms in Swine," Final Report to Animal Health Institute, submitted to FDA April 18 and April 25, 1975.

98a. Antibiotic Residue Branch Memorandum, DVR Special Project 176, August 5, 1976.

99. Bulling E., and R. Stephan, "Die Wirkung der Antibiotihabeifutterung in nutritiven Dosen auf die Resistenzentwichlung der coliformen darmflora bei Schweinen," Zentralblatt fur Veterinarmedizin; Reihe B, 19:268-284, 1972.

100. Finlayson, M., and D. A. Barnum, "The Effect of Chlortetracycline Feed Additives on the Antibiotic Resistance of Fecal Coliforms of Weaned Pigs Subjected to Experimental *Salmonella* Infection," Canadian Journal of Comparative Medicine, 37:63-69, 1973.

101. Finlayson, M., and D. A. Barnum, "The Effect of Chlortetracycline Feed Additives on Experimental *Salmonella* Infection of Swine and Antibiotic Resistance Transfer," Canadian Journal of Comparative Medicine, 37:139-146, 1973.

102. Sabo, J., and V. Kremery, "Transferable Tetracycline Resistance in *Salmonella Cholerae-suis* var. Kunzendrof," Zentralblatt fur Bakteriologic Hygine; Erste Abteilung, Originale A, 229:421-422, 1974.

103. Jarolmen, H., "Experimental and Clinical Aspects of Resistance Determinants. Experimental Transfer of Antibiotic Resistance in Swine," Annals of the New York Academy of Sciences, 182:72-79, 1971.

104. Wilcock, B. P., C. H. Armstrong, and H. J. Olamder, "The Significance of the Serotype in the Clinical and Pathological Features of Naturally Occurring Porcine Salmonellosis," Canadian Journal of Comparative Medicine, 40:80-88, 1976.

105. Groves, B. I., N. A. Fish, and D. A. Barnum, "An Epidemiological Study of *Salmonella* Infection in Swine in Ontario," Canadian Journal of Public Health, 61:396-401, 1970.

106. Voogd, C. E., P. A. M. Guinee, A. Manten, and J. J. Valkenburg, "Incidence of Resistance to Tetracycline, Chloramphenicol and Ampicillin among *Salmonella* Species Isolated in the Netherlands in 1969, 1970 and 1971," Antonie van Leeuwenhoek, 39:321-329, 1973.

107. Sojka, W. J., E. B. Hudson, G. Slavin, "A Survey of Drug Resistance in *Salmonella* Isolated from Animals in England and Wales During 1971," British Veterinary Journal, 130:128-138, 1974.

108. Sojka, W. J., G. Slavin, T. F. Brand, G. Davies, "A Survey of Drug Resistance in *Salmonellae* Isolated from Animals in England and Wales," British Veterinary Journal, 128:189-198, 1972.

109. Read, R. B., "Survey of *Salmonella* Isolates for Antibiotic Resistance," Memo to Bureau of Veterinary Medicine, November 26, 1973.

110. Gustafson, R., "Incidence and Antibiotic Resistance of *Salmonella* in Market Swine," Proceedings of Antibiotics in Animal Feeds Subcommittee of National Advisory Food and Drug Committee, Rockville, Md., January 30, 1976.

111. Smith, H. W., "Persistence of Tetracycline Resistance in Pig *E. coli*," Nature, 258:5536:628-630, 1975.

112. Linton, A., "Antibiotic Resistance: The Present Situation Reviewed," Veterinary Record, 100:354-360, 1977.

113. Larsen, J., and N. Neilsen, "Influence of the Use of Antibiotics as Additives on the Development of Drug-resistance in Intestinal *Escherichia coli* from pigs," Nordisk Veterinaermedicin, 27:353-364, 1975.

114. Smith, H. W., "Further Observations on the Effect of Chemotherapy on the Presence of Drug Resistant *Bacterium coli* in the Intestinal Tract," Veterinary Record, 70:575-580, 1958.

115. Edwards, S. J., "Effect of Antibiotics on the Growth Rate and Intestinal Flora (*Escherichia coli*) of Calves," Journal of Comparative Pathology, 72:420-432, 1962.

116. FDA Contract 71-306, University of Missouri, Final Technical Progress Report, July 1971-October 31, 1974.

116a. Huber, W. G., D. Korica, T. P. Neal, P. Schnurrenberger, and R. J. Martin, "Antibiotic Sensitivity Patterns and R-factors in Domestic and Wild Animals," Archives of Environmental Health, 22:561-567, 1971.

117. Hariharan, H., D. A. Barnum, W. R. Mitchell, "Drug Resistance Among Pathogenic Bacteria From Animals in Ontario," Canadian Journal of Comparative Medicine, 38:213-221, 1974.

118. FDA Contract 72-39, Colorado, Final Report, 1974.

119. Siegel, D., W. G. Huber, F. Enloe, "Continuous Non-Therapeutic Use of Antibacterial Drugs in Feed and Drug Resistance of the Gram-Negative enteric Florae of Food-Producing Animals," Antimicrobial Agents and Chemotherapy, 6:697-701, 1974.

120. Howe, K. and A. H. Linton, "The Distribution of O-antigen Types of *Escherichia coli* in Normal Calves, Compared with Man, and their R-plasmid Carriage," Journal of Applied Bacteriology, 40:317-330, 331-340, 1976.

121. Babcock, G. F., D. L. Berryhill, and D. H. Marsh, "R-Factors of *Escherichia coli* from Dressed Beef and Humans," Applied Microbiology, 25:21-23, 1973.

122. Burton, G. C., D. C. Hirsh, D. C. Blenden, et al., "The Effects of Tetracycline on the Establishment of *E. coli* of Animal Origin and in vivo Transfer of Antibiotic Resistance, in the Intestinal Tract of Man," Society for Applied Bacteriology Symposium Series, London, 3(0):241-253, 1974.

123. Loken, K. I., L. W. Wagner, C. L. Henke, "Transmissible Drug Resistance in *Enterobacteriaceae* Isolated From Calves Given Antibiotics," American Journal of Veterinary Research, 32:1207-1212, 1971.

124. Sato, G. and H. Kodama, "Appearance of R-factor-mediated Drug Resistance in *Salmonella typhimurium* Excreted by Carrier Calves on a Feedlot," Japan Journal of Veterinary Research, 22:72-79, 1974.

125. Falkow, S., "Infectious Multiple Drug Resistance," Pion, Ltd., London, 1975.

126. Smith, H. W., and S. Halls, "The Transmissible Nature of the Genetic Factor in *Escherichia coli* That Controls Enterotoxin production," Journal of General Microbiology, 52:319-334, 1968.

127. Smith, H. W., and M. A. Linggood, "The Transmissible Nature of Enterotoxin Production in a Human Enteropathogenic Strain of *Escherichia coli*," Journal of Medical Microbiology, 4:301-305, 1971.

128. Gorbach, S. L., "Acute diarrhea—'toxin' Disease?" New England Journal of Medicine, 283:44-45, 1970.

129. Gorbach, S. L., and C. M. Khurana, "Toxigenic *Escherichia coli*: Cause of Infantile Diarrhea in Chicago," New England Journal of Medicine, 287:791-795, 1972.

130. Dupont, H. L., S. B. Formal, and R. B. Hornick, M. J. Snyder, J. P. Lionati, D. G. Sheahan, E. H. LeBrec, and J. P. Kalas, "Pathogenesis of *Escherichia coli* Diarrhea," New England Journal of Medicine, 285:1-9, 1971.

131. Skerman, F. J., S. B. Formal, and S. Falkow, Plasmid-Association Enterotoxin Production in a Strain of *Escherichia coli* Isolated from Humans," Infection and Immunity, 5:622-624, 1972.

132. Smith, H. W., and M. A. Linggood, "The Transmissible Nature of Enterotoxin Production in a Human Enteropathogenic Strain of *Escherichia coli*," Journal of Medical Microbiology, 4:301-305, 1971.

133. Orskov, I., F. Orskov, W. J. Sojka, and J. M. Leach, "Simultaneous Occurrence of *Escherichia coli* B and L Antigens in Strains from Diseased Swine," Acta Pathologica et Microbiologica Scandinavica, 53:404-422, 1961.

134. Orskov, I., F. Orskov, W. J. Sojka, and W. Wittig, "K Antigens K88ab(L) and K88ac(L) in *E. coli*. A New O Antigen: 0141 and a New K Antigen K89(B)," Acta Pathologica et Microbiologica Scandinavica, 62:439-447, 1964.

135. Smith H. W., and M. A. Linggood, "Observations on the Pathogenic Properties of the K88 Hly and Ent Plasmids of *Escherichia coli* with Particular Reference to Porcine Diarrhea," Journal of Medical Microbiology, 4:467-485, 1971.

136. Jones, G. W. and J. M. Rutter, "Role of the K88 Antigen in the Pathogenesis of Neonatal Diarrhea Caused by *Escherichia coli* in Piglets," Infection and Immunity, 6:918-927, 1972.

137. Hohmann, A., and M. R. Wilson, "Adherence of Enteropathogenic *Escherichia*

coli to Intestinal Epithelium in Vivo," Infection and Immunity, 12:866-880, 1975.

138. Orskov, I., and F. Orskov, "Episome-Carried Surface Antigen K88 of *Escherichia coli* I. Transmission of the Determinant of the K88 Antigen and Influence on the Transfer of Chromosomal Markers," Journal of Bacteriology, 91:69-75, 1966.

139. Smith, H. W., and M. A. Linggood, "Further Observations on *Escherichia coli* Enterotoxins with Particular Regard to Those Produced by Atypical Piglet Strains and by Calf and Lamb Strains: The Transmissible Nature of These Enterotoxins and of a K Antigen Possessed by Calf and Lamb Strains," Journal of Medical Microbiology, 5:243-250, 1972.

140. Orskov, I., F. Orskov, H. W. Smith, and W. J. Sojka, "The Establishment of K99, a Thermolabile, Transmissible *Escherichia coli* Antigen, Previously Called 'Kco,' Possessed by Calf and Lamb Enteropathogenic Strains," Acta Pathologica et Microbiologica Scandinavica, 83:31-36, 1975.

141. Burrows, M. R., R. Sellwood, and R. A. Gibbons, "Haemagglutinating and Adhesive Properties Associated with the K99 Antigen of Bovine Strains of *Escherichia coli*," Journal of General Microbiology, 96:269-275, 1976.

142. Evans, D. G., R. P. Sliver, D. J. Evans, Jr., D. G. Chase, and S. L. Gorbach, "Plasmid-Controlled Colonization Factor Associated with Virulence in *Escherichia coli* Enterotoxigenic for Humans," Infection and Immunity, 12:656-667, 1975.

143. Smith, H. W., "A Search for Transmissible Pathogenic Characters in Invasive Strains of *Escherichia coli*: The Discovery of Plasmid-Controlled Toxin and a Plasmid-Controlled Lethal Character Closely Associated, or Identical, with Colicin V," Journal of General Microbiology, 83:95-111, 1974.

144. Smith, H. W., and M. B. Huggins, "Further Observations on the Association of the Colicin V Plasmid of *Escherichia coli* with Pathogenicity and with Survival in the Alimentary Tract," Journal of General Microbiology, 92:335-350, 1976.

145. Walton, J. and C. E. Smith, "Transfer of Ent Plasmids," Microbial Genetics Bulletin, 38:10, 1975.

146. Meyers, J. A., L. L. Ehnes, K. Cottingham, S. Falkow, "Incidence of Cotransfer of Ent, K99 and R-Plasmids," Microbial Genetics Bulletin, 39:13, 1975.

147. Wachsmuth, I. K., S. Falkow, and R. W. Ryder, "Plasmid-Mediated Properties of an Enterotoxigenic *Escherichia coli* Associated with Infantile Diarrhea," Infection and Immunity, 14:403-407, 1976.

148. Hefforn, F., C. Rubens, and S. Falkow, "Transportation of a Plasmid Deoxyribonucleic Acid Sequence that Mediates Ampicillin Resistance: Identity of Laboratory-Constructed Plasmids and Clinical Isolates," Journal of Bacteriology, 129:530-533, 1977.

149. Statement of the National Cattlemen's Association before the Subcommittee on Agricultural Research and General Legislation of the Senate Committee on Agriculture, Nutrition, and Forestry, September 22, 1977.

150. Testimony of the Northeast Egg Marketing Association before the Subcommitee on Agricultural Research and General Legislation of the Senate Committee on Agriculture, Nutrition, and Forestry, September 22, 1977.

151. Roberts, M. and S. Falkow, "Conjugal Transfer of R-plasmids in *Neisseria ghonorrhea*," Nature, 266:630-631, 1977.

152. Eisenstein, B., T. Sox, G. Biswas, E. Blackman, P. Spauling, "Conjugal Transfer of the Gonococcal Penicillinase Plasmid," Science, 195:998-999, 1977.

153. Elwell, L. P., J. deGraaf, D. Seibert, and S. Falkow, "Plasmid-linked Ampicillin Resistance in *Haemophilus influenzae* Type b," Infection and Immunity 12:404-410, 1975.

154. Elwell, L. P., M. Roberts, L. W. Mayer, and S. Falkow, "Plasmid Mediated B-lactamase Production in *Neisseria gonorrheae*, Antimicrobial Agents and Chemotherapy, 11:528-533, 1977.

A copy of each reference cited in this notice not appearing in journals designated by §§ 310.9 and 510.95 (21 CFR 310.9 and 510.95) is on file with the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be seen between 9 a.m. and 4 p.m. Monday through Friday.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 512, 701, 52 Stat. 1050-1051 as amended, 1055-1056 as amended, 59 Stat. 463 as amended, 82 Stat. 343-351 (21 U.S.C. 352, 357, 360b, 371)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Part 558 be amended, as follows:

1. By amending § 558.3 by adding new paragraph (b)(7) to read as follows:

§ 558.3 Definitions and interpretations.

* * * * *

(b) * * *

(7) A "restricted medicated animal feed" is a medicated animal feed which is limited to use on the order of a licensed veterinarian.

* * * * *

2. By adding new § 558.7 to read as follows:

§ 558.7 Restricted medicated animal feeds.

(a) Animal feeds containing penicillin, or chlortetracycline (except feeds for laboratory mice or psittacine birds), or oxytetracycline are restricted medicated animal feeds.

(b)(1) The manufacture of complete, restricted medicated animal feeds require an approved application pursuant to section 512(m) of the act, unless such feed is manufactured under the order of a licensed veterinarian from a restricted medicated animal feed containing 2 grams per pound of penicillin, chlortetracycline, or oxytetracycline as the sole drug in 50-pound packages.

(2) The manufacture of intermediate premixes (Type B medicated feed articles) requires an approved application pursuant to section 512(m) of the act.

(c)(1) A restricted medicated animal feed shall be dispensed only if accompanied by and in accordance with an order of a licensed veterinarian.

(2) An order by a licensed veterinarian for the dispensing of a restricted medicated animal feed shall be either a signed, written order or an oral order given directly to the party dispensing the feed who promptly reduces it to writing. All such orders must be retained at the point of sale by the party dispensing the feed for a period of not less than 2 years. The order shall include:

(i) Veterinarian's name, address, and telephone number;

(ii) Client's name and address;

(iii) Type of feed (e.g., starter, grower, finishing ration), including the quantitative level of the drug(s) involved (e.g. grams per ton);

(iv) Species to be treated, and indications for use;

(v) Total amount of feed to be mixed and number of refills permitted. The amount of feed prescribed shall not exceed the amount reasonably necessary to treat the number of animals involved; and

(vi) Date.

(d)(1) A premix (Type A medicated feed article) used in the manufacture of a restricted animal feed shall be distributed in accordance with the provisions of § 510.7 of this chapter.

(2) A restricted medicated animal feed may be distributed to a consignee who is not the user of the article if he provides the consignor with a signed statement that he will only dispense such articles to those permitted to receive them (i.e. persons having an order from a licensed veterinarian), that he will maintain the required records to establish such dispensing, and that the consignee will permit the Food and Drug Administration to inspect the records at all reasonable hours upon request by any duly authorized officer or employee of the Food and Drug Administration or other employee acting on behalf of the Secretary of Health, Education, and Welfare.

(e)(1) The label and labeling of premixes (Type A medicated feed articles), intermediate premixes (Type B medicated feed articles), and restricted medicated animal feeds containing 2 grams per pound of penicillin, chlortetracycline, or oxytetracycline in 50-pound packages shall bear, in addition to the other information required by the act, the statement "For use only in the manufacture of restricted medicated animal feeds to be used on the order of a licensed veterinarian".

(2) The label and labeling of complete restricted medicated animal feeds shall bear, in addition to the other information required by the act, the statement "For use only on the order of a licensed veterinarian".

(3) All restricted medicated animal feeds dispensed on the order of a licensed veterinarian shall be appropriately labeled for use. Such use shall include only those conditions for which the article has been approved under this part.

(f) An animal feed containing two or more animal drugs is a restricted medicated animal feed if any ingredient alone would cause a feed containing it to be a restricted medicated animal feed.

(g) A veterinarian's order is required for the dispensing of any restricted medicated animal feed 150 days after publication of a final regulation.

3. By amending § 558.15 by adding new paragraph (h) to read as follows:

§ 558.15 Antibiotic, nitrofuran, and sulfonamide drugs in the feed of animals.

* * * * *

(h) Feeds manufactured from premixes in paragraph (g)(1) or (2) of this section containing penicillin, chlortetracycline, or oxytetracycline are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

4. By amending § 558.55 by adding new paragraph (c)(3) to read as follows:

§ 558.55 Amprolium.

* * * * *

(c) * * *

(3) Feeds containing amprolium in combination with chlortetracycline or penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

5. By amending § 558.58 by revising paragraph (c) to read as follows:

§ 558.58 Amprolium and ethopabate.

* * * * *

(c) *Special considerations.* (1) Finished feeds containing amprolium and ethopabate as the sole drugs, processed from feed supplements containing not more than 0.05 percent amprolium and 0.016 percent ethopabate, and conforming to the requirements of paragraph (e) of this section are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(2) Feeds containing amprolium and ethopabate in combination with chlortetracycline or penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

6. By amending § 558.76 by revising paragraph (c)(2) and adding new paragraph (c)(3) to read as follows:

§ 558.76 Bacitracin methylene disalicylate.

* * * * *

(c) * * *

(2) Finished feeds containing bacitracin methylene disalicylate as the sole drug and conforming to the requirements of paragraph (e)(1) and (2) of this section are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(3) Feeds containing bacitracin methylene disalicylate in combination with penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

7. By amending § 558.78 by revising paragraph (c)(2) and adding new paragraph (c)(3) to read as follows:

§ 558.78 Bacitracin, zinc.

* * * * *

(c) * * *

(2) Finished feeds containing zinc bacitracin as the sole drug and conforming to the requirements of paragraph (d)(1) and (2) of this section are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(3) Feeds containing zinc bacitracin in combination with penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

8. By amending § 558.105 by revising paragraph (d) to read as follows:

§ 558.105 Buquinolate.

* * * * *

(d) *Special considerations.* (1) Maximum level permitted in medicated feed: 0.011 percent (100 grams per ton). Do not use in feeds containing bentonite.

(2) Feeds containing buquinolate in combination with chlorte-tracycline or penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

9. By amending § 558.128 by revising paragraph (c) to read as follows:

§ 558.128 Chlortetracycline.

* * * * *

(c) *Special considerations.* (1) Finished feeds containing chlortetracycline and conforming to the requirements of paragraph (e)(1) and (2) of this section and finished feeds manufactured from medicated feed articles containing 2 grams per pound chlortetracycline as the sole drug in 50-pound packages are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(2) Feeds containing chlortetracycline (except as provided in paragraph (e)(1) and (2) of this section) are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

10. By amending § 558.145 by revising paragraph (d) to read as follows:

§ 558.145 Chlortetracycline, procaine penicillin, and sulfamethazine.

* * * * *

(d) *Special considerations.* This is a restricted medicated animal feed and its distribution must be in accordance with § 558.7.

* * * * *

11. By amending § 558.155 by revising paragraph (d) to read as follows:

§ 558.155 Chlortetracycline, procaine penicillin, and sulfathiazole.

* * * * *

(d) *Special considerations.* This is a restricted medicated animal feed and its distribution must be in accordance with § 558.7.

* * * * *

12. By amending § 558.175 by adding new paragraph (f) to read as follows:

§ 558.175 Clopidol.

* * * * *

(f) *Special considerations.* Feeds containing clopidol in combination with chlortetracyline are restricted medicated animal feeds and their distribution must be in accordance with § 553.7.

* * * * *

13. By amending § 558.195 by revising paragraph (f) to read as follows:

§ 558.195 Decoquinate.

* * * * *

(f) *Special considerations.* (1) Bentonite should not be used in decoquinate feeds.

(2) Feeds containing decoquinate in combination with chlortetracycline are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

14. By amending § 558.225 by revising paragraph (c) to read as follows:

§ 558.225 Diethylstilbestrol.

* * * * *

(c) *Special considerations.* (1) Maximum level of diethylstilbestrol permitted in concentrate for cattle is 0.0044 percent.

(2) Feeds containing diethylstilbestrol in combination with either chlortetracycline or oxytetracycline are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

* * * * *

15. By amending § 558.274 by revising paragraph (c) to read as follows:

§ 558.274 Hygromycin B.

* * * * *

(c) *Special considerations.* (1) Complete chicken feeds containing hygromycin B as a sole drug, processed from feed supplements containing not more than 32 grams per ton hygromycin B, and conforming to the requirements of paragraph (e) of this section are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(2) Feeds containing hygromycin B in combination with chlortetracycline or penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

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16. By amending § 558.355 by adding new paragraph (d)(5) to read as follows:

§ 558.355 Monensin.

* * * * *

(d) * * *

(5) Feeds containing monensin in combination with oxytetracycline are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

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17. By amending § 558.365 by revising paragraph (e) to read as follows:

§558.365 Nequinate.

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(e) *Special considerations.* (1) Do not use in feeds containing bentonite.

(2) Feeds containing nequinate in combination with oxytetracycline are restricted medicated animal feeds whose distribution must be in accordance with § 558.7.

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18. By amending § 558.450 by revising paragraph (c) to read as follows:

§558.450 Oxytetracycline.

* * * * *

(c) *Special considerations.* (1) Finished feeds manufactured from medicated feed articles that contain 2 grams per pound oxytetracycline as the sole drug in 50-pound packages are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(2) Feeds containing oxytetracycline are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

(3) The amount of oxytetracycline is expressed in terms of an equivalent amount of oxytetracycline hydrochloride.

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19. By amending § 558.460 by adding new paragraph (d) to read as follows:

§558.460 Penicillin.

* * * * *

(d) *Special considerations.* (1) Finished feeds manufactured from medicated feed articles that contain 2 grams per pound penicillin as the sole drug in 50-pound packages are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(2) Feeds containing penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

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20. By amending § 558.515 by revising paragraph (d) to read as follows:

§ 558.515 Robenidine hydrochloride.

* * * * *

(d) *Special considerations.* (1) Finished feed containing robenidine hydrochloride must be fed within 50 days from the date of manufacture.

(2) Do not use in feeds containing bentonite.

(3) Feeds containing robenidine hydrochloride in combination with either chlortetracycline or oxytetracycline are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

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21. By amending § 558.680 by revising paragraph (c) to read as follows:

§ 558.680 Zoalene.

* * * * *

(c) *Special considerations.* (1) Complete poultry feeds containing zoalene as a sole drug, processed from feed supplements containing not more than 0.0375 percent zoalene, and conforming to the requirements of paragraph (e) of this section are not required to comply with the provisions of section 512(m) of the Federal Food, Drug, and Cosmetic Act.

(2) Feeds containing zoalene in combination with chlortetracycline or penicillin are restricted medicated animal feeds and their distribution must be in accordance with § 558.7.

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Interested persons may, on or before April 20, 1978, submit to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

Because of the broad public interest in and concern about the proposed restriction on the distribution of penicillin and tetracycline-containing animal feeds, the Commissioner has determined that, in addition to the 90 day comment period for receipt of written comments, two informal public hearings, in accord with the provisions of 21 CFR Part 15, should be held on the proposal in geographic areas where it will have its major impact. The purpose of the informal hearings is to provide an open forum for the presentation of information and views concerning all aspects of the proposal by interested persons, be they consumers, scientists, farmers, feed manufacturers, or representatives of manufacturers of regulated products.

In preparing a final regulation, the Commissioner will consider the administrative record of these hearings along with all other written comments received during the comment period specified in the proposal. The hearings will be held during the comment period, and the Commissioner will issue separate FEDERAL REGISTER notices announcing them when the final arrangements for their conduct are completed. The hearings will be open to the public. Any interested person who files a written notice of participation may be heard with respect to matters relevant to the issues under consideration.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an economic impact statement under Executive Order 11821 (as amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the

Hearing Clerk, Food and Drug Administration.

The Food and Drug Administration has also determined that the notices jointly pertaining to penicillin and tetracyclines in animal feeds do not comprise a major economic impact (see the FEDERAL REGISTER of June 10, 1977 (42 FR 29928), August 30, 1977 (42 FR 43770), October 21, 1977 (42 FR 56254), and this notice). A copy of the combined economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration in this docket file and in the docket files of the three other actions.

Dated: January 17, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

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